

***Remarks***

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 1-24 are pending in the application, with claim 1 being the independent claim. New claims 21-24 are sought to be added. These changes are believed to introduce no new matter, and their entry is respectfully requested. Support for the amendment can be found, *inter alia*, at Table 1 of the specification.

Based on the above amendment and the following remarks, Applicant respectfully requests that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

***Rejections under 35 U.S.C. § 103***

The Examiner has maintained the five rejections of claims 1-20 under 35 U.S.C. § 103(a). Paper No. 12, at pages 2-4. It is the Examiner's position that for each of these rejections "it would have been obvious to [use a buffer other than Tris] in light of the fact that the secondary references clearly teach using HEPES and MES to buffer antithrombin III." Paper No. 12, at page 2. The Examiner further argues that "it is inherent [in the art cited] that the same antithrombin III as claimed will be prepared." Paper No. 12, at page 2.

All of the rejections in this case should be withdrawn because:

- (1) The Examiner has not established that there would have been motivation to combine the elements of the cited art; and
- (2) There are unexpected results that rebut the Examiner's assertions as to obviousness.

***I. The Examiner Has Not Established a Prima Facie Case of Obviousness***

The above notwithstanding, the Examiner bears the burden of establishing a *prima facie* case of obviousness based upon the prior art. *See In re Piasecki*, 223 USPQ 785, 787-88 (Fed. Cir. 1984). The Examiner can satisfy this burden only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references in such a way as to produce the invention as claimed. *See In re Fine*, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988). There is no basis for concluding that an invention would have been obvious solely because it is a combination of elements that were known in the art at the time the invention was made. *See Fromson v. Advance Offset Plate, Inc.*, 755 F.2d 1549, 1556 (Fed. Cir. 1995). Instead, what is needed is a reason, suggestion, or motivation in the prior art that would motivate one of ordinary skill to combine the cited references, and that would also suggest a reasonable likelihood of success in making or using the claimed invention as a result of that combination. *See In re Dow Chem. Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988). As will be discussed in detail below, the Examiner's burden has not been satisfied.

***A. The Rejection Under 35 U.S.C. § 103(a) Over Miller-Andersson et al. In View of Cahalan et al., U.S. Patent No. 5,229,172, Cahalan et al., U.S. Patent No. 5,767,108, or JP11209399A, Good et al. and Schwinn et al., '344.***

Claims 1-20 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Miller-Andersson *et al.* in view of Cahalan *et al.*, U.S. Patent No. 5,229,172 (hereinafter "'172'"), Cahalan *et al.*, U.S. Patent No. 5,767,108 (hereinafter "'108'"), or JP 11209399A, Good *et al.* and Schwinn *et al.*, '344. Applicant respectfully traverses this rejection.

The Examiner has failed to establish a *prima facie* case of obviousness because the references, even when combined, do not result in the claimed invention and there would have been no motivation to combine the references. Miller-Andersson *et al.* does not disclose (1) a process for the preparation of *latent* antithrombin III (ATIII), (2) the use of *sulfate* ions, or (3) the use of a Good's buffer other than Tris.

Miller-Andersson *et al.* relates to the use of persulfate ions ( $S_2O_8^{2-}$ ), which are distinct from the sulfate ions ( $SO_4^{2-}$ ) used in the present invention. In Miller-Andersson *et al.*, ammonium persulfate is used as a catalyst for polymerization of the gel for the electrophoresis methods described. See Miller-Andersson *et al.* at page 442. In contrast, sulfate ions are used in the present invention in the buffer for incubating native antithrombin III. Neither gel electrophoresis nor persulfate ions are part of the claimed invention. A person of ordinary skill in the art would not have been motivated to use ammonium persulfate in a method for purifying a protein because ammonium persulfate is an oxidizing agent and thus would be expected to destroy the structure of antithrombin III by oxidizing S-S bonds. *We previously pointed out this difference and the Examiner has failed to overcome this flaw in the rejection.*

The secondary references, Cahalan *et al.*, '172, Cahalan *et al.*, '108, or JP 11209399A, Good *et al.* and Schwinn *et al.*, '344, do not cure the deficiencies in Miller-Andersson *et al.* and none of the references provide motivation to combine the relevant disclosures.

The Cahalan references and JP 11209399A merely disclose that antithrombin III is contacted with MES and HEPES buffers. There would have been no motivation to substitute MES or HEPES buffers for the Tris-HCl disclosed in Miller-Andersson *et al.* The Examiner asserts that "the secondary references clearly teach using HEPES and

MES to buffer antithrombin." Paper No. 12, at page 2 (emphasis added). However, neither the Cahalan references nor JP 11209399A discloses that MES or HEPES should be used to precipitate latent antithrombin III. Therefore, Cahalan *et al.*, '172, Cahalan *et al.*, '108 and JP 11209399A do not cure the deficiencies in Miller-Andersson *et al.*

Good *et al.* merely discloses a class of zwitterionic buffers. Good *et al.* does not disclose that these buffers should be used in a method for preparing *latent* antithrombin III from *native* antithrombin III. Good *et al.* does not support the Examiner's assertion that it would have been obvious to use a buffer other than Tris because "the secondary references clearly teach using HEPES and MES to buffer antithrombin III." Paper No. 12, at page 2. To the contrary, Good *et al.* teaches away from replacing a Tris buffer with MES, stating that it is "*ludicrous to compare Tris with MES...since their buffering ranges do not overlap and they could never be considered as alternatives.*" Good *et al.* at page 477. Thus, Good *et al.* does not cure the deficiencies in Miller-Andersson *et al.*

Schwinn *et al.*, '344 has the same deficiencies as Miller-Andersson *et al.* Schwinn *et al.*, '344, does not disclose (1) a process for the preparation of *latent* antithrombin III and (2) the use of a Good's buffer other than Tris. Thus, Schwinn *et al.*, '344 does not cure the deficiencies in Miller-Andersson *et al.* Further, there would have been no reason to combine two references which are equally deficient.

The Examiner has failed to establish a *prima facie* case of obviousness. *There is no objective teaching in the prior art or a showing that the knowledge generally available to one of ordinary skill in the art would have led that individual to combine the relevant teachings of the references to arrive at the presently claimed invention.* Nothing in the Office Action points to such a teaching. Further, even if there had been motivation to combine the references, the combination does not result in the presently

claimed invention because the cited references, even in combination, fail to teach or suggest a method for preparing *latent* antithrombin III by using *sulfate* ions. Accordingly, Applicant respectfully requests that the rejection under 35 U.S.C. § 103(a) over Miller-Andersson *et al.* in view of Cahalan *et al.*, '172, Cahalan *et al.*, '108, or JP 11209399A, Good *et al.* and Schwinn *et al.*, '344, be withdrawn.

**B. The Rejection Under 35 U.S.C. § 103(a) Over Eibl *et al.*, '232, In View of Cahalan *et al.*, '172, Cahalan *et al.*, '108, or JP 11209399A, Miller-Andersson *et al.*, Good *et al.* and Schwinn *et al.*, '344.**

Claims 1-20 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Eibl *et al.*, '232, in view of Cahalan *et al.*, '172, Cahalan *et al.*, '108, or JP 11209399A, Miller-Andersson *et al.*, Good *et al.* and Schwinn *et al.*, '344. Applicant respectfully traverses this rejection.

The Examiner has failed to establish a *prima facie* case of obviousness because the references, even when combined, do not result in the claimed invention and there is no motivation to combine the references. Eibl *et al.*, '232, does not disclose (1) a process for the preparation of *latent* antithrombin III and (2) the use of a Good's buffer other than Tris. The secondary references, Cahalan *et al.*, '172, Cahalan *et al.*, '108, or JP 11209399A, Miller-Andersson *et al.*, Good *et al.* and Schwinn *et al.*, '344, do not cure the deficiencies in Eibl *et al.*, '232 and none of the references provide motivation to combine the relevant disclosures.

The deficiencies in Eibl *et al.*, '232 are similar to those in Miller-Anderson *et al.*, which deficiencies have been addressed in Section I(A) above. Since Eibl *et al.*, '232 and Miller-Anderson *et al.* share the same deficiencies, there would have been no reason to combine two references which are equally deficient. The disclosures of Cahalan *et al.*,

'172, Cahalan *et al.*, '108, JP 11209399A, Good *et al.* and Scwhinn *et al.*, '344, their relationship to the present claims, and their failure to provide motivation to combine have been discussed in Section I(A) above. All the secondary references fail to disclose (1) a process for the preparation of *latent* antithrombin III and (2) the use of a Good's buffer other than Tris and therefore fail to cure the deficiencies in Eibl *et al.*, '232.

The Examiner has failed to establish a *prima facie* case of obviousness. There is no objective teaching in the prior art or a showing that the knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references to arrive at the presently claimed invention. *Where in the art is it taught that latent antithrombin III can be prepared by incubating native antithrombin III with the combination of sulfate ions and a Good's buffer other than Tris?* Further, even if there were motivation to combine the references, the combination does not result in the presently claimed invention because the cited references fail to suggest a method for preparing latent antithrombin III. Accordingly, Applicant respectfully requests that the rejection under 35 U.S.C. § 103(a) over Eibl *et al.*, '232, in view of Cahalan *et al.*, '172, Cahalan *et al.*, '108, or JP 11209399A, Miller-Andersson *et al.*, Good *et al.* and Schwinn *et al.*, '344, be withdrawn.

**C.     *The Rejection Under 35 U.S.C. § 103(a) Over Schwinn et al. '603, Schwinn et al. '794, or Schwinn et al. '187, In View of Eibl et al., '084 or Schwinn et al., '344, Cahalan et al., '172, Cahalan et al., '108, or JP 11209399A, Miller-Andersson et al., and Good et al.***

Claims 1-20 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Schwinn *et al.*, '603, Schwinn *et al.*, '794 or Schwinn *et al.*, '187, in view of Eibl *et al.*,

'084, or Schwinn *et al.*, '344, Cahalan *et al.*, '172, Cahalan *et al.*, '108, or JP 11209399A, Miller-Andersson *et al.*, and Good *et al.* Applicant respectfully traverses this rejection.

The Examiner has failed to establish a *prima facie* case of obviousness because the references, when combined, do not result in the claimed invention and there would have been no motivation to combine the references. The Schwinn references ('603, '794 or '187) do not disclose (1) a process for the preparation of *latent* antithrombin III and (2) the use of a Good's buffer other than Tris. The secondary references, Eibl *et al.*, '084 or Schwinn *et al.*, '344, Cahalan *et al.*, '172, Cahalan *et al.*, '108, or JP 11209399A, Miller-Andersson *et al.*, and Good *et al.*, do not cure the deficiencies in the Schwinn references ('603, '794 or '187) and none of the references provide motivation to combine the relevant disclosures.

The deficiencies in the Schwinn references ('603, '794 or '187) are similar to those in Miller-Anderson *et al.*, which deficiencies have been addressed in Section I(A) above. The disclosures of Cahalan *et al.*, '172, Cahalan *et al.*, '108, JP 11209399A, Good *et al.* and Schwinn *et al.*, '344, their relationship to the present claims, and their failure to provide motivation to combine have been discussed in Section I(A) above. Eibl *et al.*, '084 also fails to disclose (1) a process for the preparation of *latent* antithrombin III and (2) the use of a Good's buffer other than Tris. Since the Schwinn references ('603, '794 or '187) share the same deficiencies with Eibl *et al.*, '084 and Miller-Anderson *et al.*, there would have been no reason to combine these references which are equally deficient. All the secondary references fail to disclose (1) a process for the preparation of *latent* antithrombin III and (2) the use of a Good's buffer other than Tris and therefore fail to cure the deficiencies in the Schwinn references ('603, '794 or '187).

The Examiner has failed to establish a *prima facie* case of obviousness. There is no objective teaching in the prior art or a showing that the knowledge generally available to one of ordinary skill in the art would have led that individual to combine the relevant teachings of the references to arrive at the presently claimed invention. Further, even if there was motivation to combine the references, the combination does not result in the presently claimed invention because the cited references fail to suggest a method for preparing latent antithrombin III. Accordingly, Applicant respectfully requests that the rejection under 35 U.S.C. § 103(a) over Schwinn *et al.*, '603, Schwinn *et al.*, '794 or Schwinn *et al.*, '187, in view of Eibl *et al.*, '084, or Schwinn *et al.*, '344, Cahalan *et al.*, '172, Cahalan *et al.*, '108, or JP 11209399A, Miller-Andersson *et al.*, and Good *et al.*, be withdrawn.

***D. The Rejection Under 35 U.S.C. § 103(a) Over Eibl et al., '084, In View of Cahalan et al., '172, Cahalan et al., '108, or JP 11209399A, Miller-Andersson et al. and Good et al.***

Claims 1-20 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Eibl *et al.*, '084, in view of Cahalan *et al.*, '172, Cahalan *et al.*, '108, or JP 11209399A, Miller-Andersson *et al.* and Good *et al.* Applicant respectfully traverses this rejection.

The Examiner has failed to establish a *prima facie* case of obviousness because the references, when combined, do not result in the claimed invention and there is no motivation to combine the references. As stated in Section I(C) above, Eibl *et al.*, '084, does not disclose (1) a process for the preparation of *latent* antithrombin III and (2) the use of a Good's buffer other than Tris. The secondary references, Cahalan *et al.*, '172, Cahalan *et al.*, '108, or JP 11209399A, Miller-Andersson *et al.* and Good *et al.* do not



cure the deficiencies in Eibl *et al.*, '084 and none of the references provide motivation to combine the relevant disclosures.

As discussed in Section I(C) above, the deficiencies in Eibl *et al.*, '084 are similar to those in Miller-Anderson *et al.*; which deficiencies have been addressed in Section I(A) above. Since Eibl *et al.*, '084 and Miller-Anderson *et al.* share the same deficiencies, there is no reason to combine two references which are equally deficient. The disclosures of Cahalan *et al.*, '172, Cahalan *et al.*, '108, JP 11209399A, and Good *et al.*, their relationship to the present claims, and their failure to provide motivation to combine have been discussed in Section I(A) above. All the secondary references fail to disclose (1) a process for the preparation of *latent* antithrombin III and (2) the use of a Good's buffer other than Tris and therefore fail to cure the deficiencies in Eibl *et al.*, '084.

The Examiner has failed to establish a *prima facie* case of obviousness. There is no objective teaching in the prior art or a showing that the knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references to arrive at the presently claimed invention. Further, even if there was motivation to combine the references, the combination does not result in the presently claimed invention because the cited references fail to suggest a method for preparing latent antithrombin III. Accordingly, Applicant respectfully requests that the rejection under 35 U.S.C. § 103(a) over Eibl *et al.*, '084, in view of Cahalan *et al.*, '172, Cahalan *et al.*, '108, or JP 11209399A, Miller-Anderson *et al.* and Good *et al.*, be withdrawn.

***E. The Rejection Under 35 U.S.C. § 103(a) Over Schwinn et al., '344, In View of Cahalan et al., '172, Cahalan et al., '108, or JP 11209399A, Miller-Andersson et al. and Good et al.***

Claims 1-20 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Schwinn *et al.*, '084, in view of Cahalan *et al.*, '172, Cahalan *et al.*, '108, or JP 11209399A, Miller-Andersson *et al.* and Good *et al.* Applicant respectfully traverses this rejection.

The Examiner has failed to establish a *prima facie* case of obviousness because the references, when combined, do not result in the claimed invention and there is no motivation to combine the references. As stated in Section I(A) above, Schwinn *et al.*, '344, does not disclose (1) a process for the preparation of *latent* antithrombin III and (2) the use of a Good's buffer other than Tris. The secondary references, Cahalan *et al.*, '172, Cahalan *et al.*, '108, or JP 11209399A, Miller-Andersson *et al.* and Good *et al.* Miller-Andersson *et al.* do not cure the deficiencies in Schwinn *et al.*, '344 and none of the references provide motivation to combine the relevant disclosures.

As discussed in Section I(A) above, the deficiencies in Schwinn *et al.*, '344 are similar to those in Miller-Anderson *et al.*; which deficiencies have been addressed in Section I(A) above. Since Schwinn *et al.*, '344 and Miller-Anderson *et al.* share the same deficiencies, there would have been no reason to combine two references which are equally deficient. The disclosures of Cahalan *et al.*, '172, Cahalan *et al.*, '108, JP 11209399A, and Good *et al.*, their relationship to the present claims, and their failure to provide motivation to combine have been discussed in Section I(A) above. All the secondary references fail to disclose (1) a process for the preparation of *latent* antithrombin III and (2) the use of a Good's buffer other than Tris and therefore fail to cure the deficiencies in Schwinn *et al.*, '344.

The Examiner has failed to establish a *prima facie* case of obviousness. There is no objective teaching in the prior art or a showing that the knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references to arrive at the presently claimed invention. Further, even if there was motivation to combine the references, the combination does not result in the presently claimed invention because the cited references fail to suggest a method for preparing latent antithrombin III. Accordingly, Applicant respectfully requests that the rejection under 35 U.S.C. § 103(a) over Schwinn *et al.*, '344, in view of Cahalan *et al.*, '172, Cahalan *et al.*, '108, or JP 11209399A, Miller-Andersson *et al.* and Good *et al.*, be withdrawn.

***II. The Rejections Under 35 U.S.C. § 103(a) are Rebutted by Evidence of Unexpected and Surprising Results.***

The above notwithstanding, assuming for the sake of argument that *prima facie* obviousness had been established for any rejected claim, the evidence of unexpected results discussed below would rebut such a finding.

When performing an obviousness analysis, objective evidence of nonobviousness must be considered, if present. *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538, 218 USPQ 871, 879 (Fed. Cir. 1983). However, although "objective evidence [of] non-obviousness must be commensurate in scope with the claims which the evidence is offered to support" (*In re Grasselli*, 713 F.2d 731, 743, 218 USPQ 769, 778 (Fed. Cir. 1983)(quoting *In re Tiffin*, 448 F.2d 791, 171 USPQ 294 (CCPA 1971)), an applicant need not show unexpected results for every embodiment within the scope of the claims (*See Ex parte Winters*, 11 USPQ2d 1387, 1388 (Bd. Pat. App. & Int. 1989)). Instead,

patentability may be established by showing unexpected superiority for embodiments that are representative of the embodiments covered by the scope of the claims. *See Ex parte Winters*, 11 USPQ2d at 1388.

Wardell *et al.* (Biochemistry 36:13133-13142, 1997) described preparation of latent antithrombin III using an incubation buffer of 10 mM Tris-HCl and 0.25 M citrate. *See* specification, page 2, paragraph [0005]. In experiments described in the present application, the preparation of latent antithrombin III with a HEPES/ammonium sulfate buffer was compared to preparation with the Tris-HCl/citrate buffer of Wardell *et al.* In each of these experiments, preparation of latent antithrombin III with a HEPES/ammonium sulfate buffer resulted in an unexpectedly superior yield of latent antithrombin when compared to experiments conducted with the Tris-HCl/citrate buffer.

In the experiments set forth in the present application and performed in accordance with the invention, antithrombin was incubated in either 5 mM or 25 mM HEPES and 0.8-250 mM ammonium sulfate, or in 10 mM Tris-HCl and 0.5 M trisodium citrate, and then separated using heparin affinity chromatography. *See* specification page 6, paragraph [0021]-page 7, paragraph [0025]. Integration of the low heparin binding peak indicated a 44% yield of latent antithrombin III for samples prepared in a Tris-HCl/citrate buffer, compared to incubation in 0.9 and 0.8 M ammonium sulfate in HEPES which yielded 71% and 89%, respectively. *See* Figure 1, Table 1 and page 8, paragraph [0028]. As shown by Table 1 of the specification, decreasing concentrations of ammonium sulfate result in increasing yields of antithrombin III. *Such high yields of antithrombin III are unexpected in view of the cited art.*

The results from these experiments demonstrate unexpected and surprising results for preparation of latent antithrombin III with a HEPES/ammonium sulfate buffer,

compared to using the Tris-HCl/citrate buffer of the art. The evidence of unexpected and surprising results rebuts a finding of *prima facie* obviousness. For this reason as well as the reasons stated above, the rejection of claims 1-20 as obvious should be withdrawn.

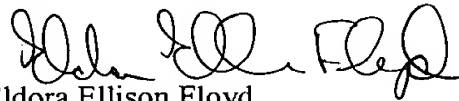
### ***Conclusion***

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicant therefore respectfully requests that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicant believes that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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